**Research Proposal:**

# Dissociation in Functional Connectivity of the Posterior and Anterior Parahippocampal Cortex for Spatial and Non-spatial Processing

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The parahippocampal cortex (PHC) has received a great deal of interest in cognitive neuroscience research. This largely stems from profound activation of this area observed during tasks that promote spatial processing. Indeed, one region within the PHC seemingly demonstrates such a degree of selective activity while viewing scenes that it has been termed the parahippocampal place area (PPA; Epstein & Kanwisher, 1998). Furthermore, severe impairment in spatial memory tasks has been reported within participants demonstrating selective lesions confined to the PHC (Ploner et al., 2000). Such evidence has led researchers to propose that the PHC performs a critical role in spatial cognition (Epstein & Vass, 2014).

A dominant framework to emerge from the reliable findings linking spatial cognition to the PHC is the spatial layout hypothesis (Epstein, 2008). Researchers adopting this position argue that the fixed geometry of a scene elicits neural activity within the PPA (Epstein & Kanwisher, 1998; Epstein, 2008). In this sense, the PPA is not responsible for processing scenes specifically, but rather supports the recognition of more general background features, which are notably present within all scenes.

A considerable body of research supporting the spatial layout hypothesis has been generated. PPA activity is reported to remain consistent while viewing indoor scenes with contained objects rearranged to generate different relational configurations, or even when removed entirely (Epstein & Kanwisher, 1998; Epstein & Ward, 2010). Lego constructions replicating scenes are found to produce greater PPA activation than objects similarly composed of Legos (Epstein et al., 1999). Likewise, when fixed elements of scenes are rearranged to distort the sense of three-dimensional space, PPA activity is cited to decrease (Epstein & Kanwisher,

1998). These findings form a convincing case that the PHC (PPA, specifically) is involved in encoding very general, fixed, geometric properties within the environment. Indeed, smaller elements constituting a scene, such as objects, appear to be inconsequential in influencing the activity within the PHC (Epstein, 2008), implying that the PHC performs a specialized role in spatial processing.

Another line of evidence seemingly runs contrary to the interpretations of the spatial layout hypothesis, suggesting that the essential role of the PHC lies in episodic memory. This alternative is intuitive given that the PHC is situated within the medial temporal lobes. These medial structures are well established as performing important roles within the realm of declarative memory, which includes long-term episodic ability (Lech & Suchan, 2013). The PHC has been found to be recruited during episodic encoding (Schacter & Wagner, 1999), therefore, PHC activity has been implicated in the encoding of associations that constitute a particular episode. Importantly, associations within an episode need not be limited to spatial elements. Any features present during the encoding of an episode may be associated with the memory. Episodic associations, therefore, would include elements such as sounds, smells, and affect, strictly non-spatial features. Findings consistent with this hypothesis have been generated. For instance, PHC activity has been demonstrated during the encoding of associated objects (Hales et al., 2009), and has been found to be positively correlated with the amount of detail (i.e. elements associated with the episode) when retrieving a memory (Tendolkar et al., 2008). Such findings pose a notable challenge to the spatial layout hypothesis, and any model of PHC function must reconcile these two well-established streams of research.

Bar and colleagues (2008) offer a model that potentially unifies the divergent findings regarding the PHC. They suggest that PHC activation reflects an underlying role in processing

contextual associations, both spatial and non-spatial. The generation of contextual associations plays an undeniable role in the creation of an episodic memory. That is, one must not only remember the facts of an event, but also bind this information with the context (environment, one's mood, etc.) in which it was encountered in order to produce an episodic representation. This provides a possible explanation for findings linking PHC activity with episodic encoding. Similarly, scenes form a context of various elements (e.g. buildings, trees, walls) associated with specific coordinates within a frame of view. Experiments manipulating contextual processing have associated this function with the PHC (Bar & Aminoff, 2003; Aminoff, 2008; Diana, Yonelinas & Ranganath, 2013). Consequently, the abundant findings implicating PPA activation in landmark recognition (Epstein & Vass, 2014) are interpreted as reflecting the processing of associations amongst elements forming the context of a particular scene.

Bar and colleagues (2008) further propose that the processing of spatial versus non-spatial contextual information is divided within the PHC. That is, the pPHC is noted to perform an important role in the processing of spatial contextual associations, while the aPHC is suggested to engage in processing non-spatial contextual information. Evidence for such a differentiation in function is supported by a considerable body of literature (Aminoff, Kveraga & Bar, 2013). Viewing famous faces, highly contextualized but non-spatial stimuli, has been found to elicit activity within the aPHC (Bar, Aminoff & Ishai, 2008). Moreover, differential activation within the PHC has been observed while presenting participants with strongly spatially contextualized objects and strongly non-spatially contextualized objects (Bar & Aminoff, 2003). Stimuli such as traffic lights are strongly associated with a particular space (i.e. intersections), and therefore are noted to associated strongly with a spatial context. Meanwhile, objects such as a sunglasses are strongly tied to a context (i.e. sunny days, warm weather, summer, etc.), but not

a specific spatial associate, as they may appear in many different locations. It was found that viewing stimuli with strong spatial contexts was associated with increased activity within the pPHC, conversely, viewing stimuli with strong non-spatial contexts corresponded with increases in aPHC activity.

Another study (Aminoff, Gronau & Bar, 2007) required participants to study arrays that included spatial, non-spatial, and no contextual information. Spatial contexts were achieved through constructing arrays comprising objects appearing in the same position on each presentation in the study period. Non-spatial contexts constituted arrays presenting a set of objects that remained constant, but varied in spatial location between presentations. When tested, objects that appeared within the spatial context condition evoked activity in the pPHC, while the aPHC was observed to be recruited when tested on objects from the non-spatial array. Altogether, neuroimaging data is supportive of the contextual associations hypothesis of the PHC, and a growing body of research indicates a spatial/non-spatial hierarchy of processing within this medial temporal region.

The PHC, however, is not the only cortical site that has been implicated in the processing of contextual associations. Indeed, two other regions, the retrosplenial cortex and the medial prefrontal lobe have been found to also contribute to this function (Bar & Aminoff, 2003; Aminoff et al., 2013). The PHC has been found to interact with these regions, supporting the proposal of a contextual processing role of the PHC. Strong evidence comes from magnetoencephalography data (Kveraga et al., 2011), where MEG signal was found to first appear above the PHC, which subsequently phase-locked with RSC activity, and, finally, RSC activity was found to then phase-lock with the MPFC. Kveraga and colleagues (2011) suggested that these three regions, while all processing information key to contextual associations, each

process different aspects of the contexts such as processing stimulus context, abstracted "context-frames," and performing a prospective role in using the current context to predict future outcomes.

Despite the apparent parsimony of Bar and colleagues (2008) framework, little agreement has been reached in the domain of PHC research. Neuroimaging studies are useful; however activation patterns may support various divergent interpretations. One approach to test these interpretations is through investigation of neural connectivity. Cortical regions that are acknowledged as supporting the same, or related, functions should be strongly connected to one another. Therefore, the main interpretations of PHC function (i.e. spatial cognition, episodic encoding, and contextual association) may be supported through examination of which other sites to which this structure is most connected.

The contextual association hypothesis generates specific predictions regarding the connectivity of the PHC. Consistent with the contextual association hypothesis, it is predicted the PHC is in fact crucial in processing contextual associations, and comparison of this region's activity during spatial vs. non-spatial contextual tasks will reveal a parietal/anterior dissociation. Furthermore, it is predicted that investigation will reveal that this region demonstrates strong functional connections with both the RSC and MPFC, forming a context network. However, the aPHC and pPHC are predicted to exhibit differential connectivity with other brain regions. That is, given the proposed spatial/non-spatial hierarchy of the PHC, the pPHC should consistently be shown to exhibit strong parietal connections, suggesting a more specialized role in processing spatial information.

# Methods

## Participants

The proposed study aims to recruit a sample comprising 50 healthy university students. A short questionnaire will be provided to participants in order to screen for past trauma, which may affect brain function. Informed consent will be obtained upon arrival.

## Procedure

Participants will enter an fMRI scanner and complete a battery of tasks. Spontaneous activity of the identified sites will then be compared with the PHC. The aim in localizing these regions individually, rather than examining coordinates known on average to constitute these structures, is to improve accuracy in inferring connectivity. By delineating these regions within each individual, correlations between sites investigated will exhibit greater validity, and the likelihood of detecting connections is increased. Participants will be presented first with a contextual processing task (to localize the aPHC and pPHC for use as seeds, and to investigate if a spatial/non-spatial distinction in PHC activity is replicated), followed by tasks known to promote activity of the RSC, MPFC, and parietal cortex.

**Parahippicampal cortex.** Imaging of the PHC will be accomplished through the use of the task described in Aminoff and colleagues' (2007) study. This task requires participants learn visual arrays associated with spatial and non-spatial contexts. This distinction will allow for the localization of the pPHC and aPHC in participants during spatial and non-spatial contexts, respectively.

**Retrosplenial cortex.** Retrosplenial activation has been consistently shown through tasks requiring orientation and use of long-term knowledge (Epstein et al., 2013). Therefore, to localize the RSC, an orientation task, like that used by Epstein, Parker, and Feiler (2007), will be

employed. In this task, participants are required to make judgements regarding the location of a familiar scene (i.e. cardinal direction in relation to a reference point) or which direction a familiar scene is facing.

**Medial prefrontal cortex.** The MPFC will be identified within participants using a self-referential task, described by Gusnard et al. (2001), and found to promote MPFC activity. This task involves the presentation of pictorial stimuli and the subsequent requirement for participants to indicate whether the stimulus made them feel pleasant or unpleasant. Compared to external judgement (i.e. whether the picture was indoors or outdoors), internal appraisals were found to consistently activate the MPFC.

**Parietal cortex.** An abundance of evidence indicates that selective parietal regions are activated during spatial tasks (Corbetta et al., 1993; Jonides et al., 1993). Therefore, parietal sites engaged in spatial process will be imaged in order to investigate whether this region is more strongly connected to the pPHC. To do so, a simple location matching task, shown to recruit activity within parietal regions will be employed (Haxby et al., 1994). In this task, participants are presented with three stimuli. A sample stimulus is situated above two choice-stimuli. Each stimulus consists of a large square containing a smaller square. The larger square contains a bar along one edge (right edge on samples and bottom edge on choices). Participants must indicate which of the choice stimuli's smaller square occupies the same space within the larger square, relative to the edge-bar, as the sample.

**fMRI Analyses**

fMRI data will be analyzed by way of multivoxel pattern analysis and resting state functional connectivity. Both approaches offer unique ways of testing the predictions generated by the contextual associations hypothesis.

**Multivoxel pattern analysis.** Multivoxel pattern analysis (MVPA) will be used to discern PHC activity during a contextual processing task (Aminoff et al., 2007). As a multivariate method, MVPA is capable of identifying dissociable patterns of brain activity corresponding to different tasks (Norman et al., 2006). This approach allows for the specific examination of voxels comprising the PHC. The respective patterns of activity characterizing spatial vs. non-spatial contextual trials may then be used to determine whether activity in these conditions is distinct, as predicted. In particular, MVPA is able to identify whether respective patterns are more weighted to anterior or posterior regions, making it an ideal means of investigating this hypothesis.

**Resting state functional connectivity.** Resting state functional connectivity (RSFC) provides a novel methodology for addressing the predicted differential processing of the aPHC and pPHC. This approach has been used to investigate similar questions of specialized cortical function (Stevens et al., 2012; Stevens & Spreng, 2014), and may similarly offer insight into functional distinctions within the PHC. This method captures fMRI images of the participant's brain activity during a resting state. Spontaneous activity may then be correlated with a seed, or region of interest, in order to infer functional connections within the brain. The aPHC and pPHC will be separately used as seeds. Resting activity of each region will then be compared to activity of the individually localized RSC, MPFC, and parietal cortex. Based on the contextual associations hypothesis, both seeds should correlate highly with the RSC and MPFC, implying a contextual role. However, the pPHC should exhibit a greater correlation with parietal regions, given its proposed role in spatial processing.

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